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Theodore Gottlieb

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

SERIAL NO.	: 09/454,740
APPLICANT	: Timo HILLEBRAND et al.,
FILED	: December 6, 1999
EXAMINER	: A. Chakrabarti
ART UNIT	: 1655
FOR	: **FORMULATIONS AND METHOD FOR ISOLATING NUCLEIC ACIDS FROM OPTIONAL COMPLEX STARTING MATERIALS AND SUBSEQUENT COMPLEX GENE ANALYSIS**

Hon. Assistant Commissioner of Patents
Washington, D.C. 20231

May 31, 2002

PRELIMINARY AMENDMENT AND RESPONSE

Sir:

This communication is in response to the Final Action of February 1, 2002.

The Applicants respectfully request consideration of the comments submitted herewith prior to further examination on the merits.

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefore. Please charge the required fee to Deposit Account No. 14-1263.

ADDITIONAL FEES

Please charge any further insufficiency of fees, or credit any excess to Deposit Account No. 14-1263.

REMARKS

Claims 1-5, 7-11 and 26-29 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Anderson et al., (U.S. Patent 5,948,656) ("Anderson"), in view of Cleuziat et al., (U.S. Patent 5,824,517) ("Cleuziat"), Nochumson et al., (U.S. Patent 5,552,325) ("Nochumson"), and other secondary references of record.

In response, the Applicants' submit concise remarks illustrating critical errors in the factual analysis of the Examiner's citations. These remarks comprise the Applicants' analysis and responses thereto, of the facts disclosed within the Examiner's citations. In brief, it is now clear that the Examiner has misinterpreted the disclosures of Anderson, and Nochumson and, accordingly, has developed an incorrect and improper basis for rejecting the claims.

Applicants' Invention

The claimed formulations are directed to components that act together to (1) lyse or solubilize DNA-containing cell and tissue samples, and (2) promote the binding of the DNA to insoluble supports for rapid and quantitative isolation of DNA.

A key inventive feature of the formulation is that the Applicants achieve these goals without employing chaotropic salt components in order to promote lysing the sample and DNA binding to a support. Chaotropic salts disrupt the binding of water to DNA, thus forcing it out of solution and making it energetically more favorable for the DNA to bind an insoluble support.

The most common chaotropes used in DNA isolations are guanidine isothiocyanate, and NaI. It is important to note that with respect to chaotropic strength SCN^- and I^- and considered strong chaotropic anions.

In contrasts, anions such as sulfate and citrate, are among the most weakly chaotropic, and are listed on the other extreme end of the Hofmeister spectrum. In fact, these anions are not considered chaotropic but kosmotropic. In the chemical arts these "anti-chaotropes" are referred to as *kosmotropes*, i.e., "structure-makers." Such compounds do not disrupt the ability of water to hydrogen bond to DNA, and thus, promote binding to the insoluble supports by a different mechanism.

The Applicants have used the term anti-chaotrope (as opposed to kosmotrope) to describe the lack of "structure-breaking" properties. Commonly used species such as chloride ion, and NaCl, are in the middle of the spectrum and are considered mildly chaotropic agents, but not anti-chaotropes.

In brief, Applicants' formulations are novel and unobvious over the cited references. This conclusion is supported by the fact that the cited principal references teach away from the claimed formulations, and from each other. This is explained in detail in the following remarks.

Anderson *Expressly* Teaches Away From the Applicants' Claims

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983).

In addition, "[a] reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re* Gurley, 31 USPQ2d 1130 (Fed. Cir. 1994). In other words, if a reference would have discouraged the ordinary skilled artisan from taking a research path, then the reference is teaching away.

Applicants respectfully suggest that when Anderson is viewed in its entirety according to *Garlock*, it is indisputable that it teaches away from the claims.

The Examiner cites Anderson, column 15, lines 23-27 for teaching a lysis/binding buffer system for purifying plasmid DNA from yeast colonies that contains at least one anti-chaotropic salt. This disclosure comprises the principal reference and contributes substantially to the claims' alleged unpatentability. As demonstrated below, the Examiner's conclusion that this disclosure's teaching renders the claims obvious is clearly incorrect.

In the cited text, Anderson's method includes the following steps:

- lysing yeast colonies in a detergent solution containing a *non*chaotropic salt (as opposed to Applicants' *anti-chaotropic*);
- adding glass beads (and phenol/chloroform) to the extract while agitating the tube;
- centrifuging the tube;
- removing the supernatant from the pellet material, that contains the glass beads and cell debris; and
- precipitating the DNA from the supernatant with alcohol.

Applicants assert that if Anderson's buffer conditions were even remotely similar to the Applicants', **the DNA would have been recovered in the glass bead pellet in a manner very similar to the result obtained when using the Applicants' formulation.** See Applicants' Example 2, lines 13-15; Example 7, lines 13-15/Figure

7; Example 9, lines 33-35. However, under Anderson's conditions, the DNA does not bind to the glass beads, but remains in the supernatant for subsequent alcohol precipitation.

It is further noted, that one with ordinary skill in yeast cloning methods would immediately appreciate that the presence of glass beads is to facilitate the mechanical disruption of the yeast cells during the vortexing step. See col. 15, line 27. They are not intended to bind DNA. In fact, this procedure is used precisely because under Anderson's conditions, the DNA does not bind the glass beads. If the DNA bound to the beads, the procedure would not be useful because doing so would significantly decrease the yield of DNA from the supernatant. Therefore, in the presence of an insoluble support, i.e., glass beads, Anderson's compositions actually constitute DNA *anti-binding* buffers.

Such a composition cannot reasonably be viewed as rendering the Applicants' formulations obvious.

Anderson's completely contradictory results comprise a clear teaching away from the Applicants' results obtained with the claimed formulation. In other words, had Anderson employed the Applicants' lysis/binding formulation, the DNA would have bound the beads – opposite to that found by Anderson.

This constitutes teaching away as set forth in *Gurley*, because one with ordinary skill in the art would clearly be discouraged from using Anderson's DNA *anti-binding* buffer to attempt to arrive at Applicants' formulations that *promote* DNA binding to various supports, including glass beads.

The Applicants respectfully request that the rejections under § 103(a) of all the claims based on Anderson be withdrawn in view of the foregoing discussion, and further in view of Federal Circuit jurisprudence holding that if a first prior art reference "did in fact teach away...then that finding alone can defeat obviousness." Winner International Royalty Corp. v. Wang. 202 f.3d 1340 (Fed. Cir. 2000).

Neither Cleuziat, Nochumson, nor Gonsalves can Cure Anderson's Defect

Examiner asserts *In re Keller* for the proposition that one cannot argue against an obviousness rejection by attacking references individually, where rejections are based on combinations of references. Final Action, page 10, item 8. However, the Examiner's citation of *Keller* is not in the appropriate context, and thus, is not a proper basis to maintain the rejection.

Keller cautions against arguing against the features of a reference, rather than the combination of features. A more complete rendering of *Keller* states that, "[t]he test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.... Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). (Emphasis added).

Therefore, it follows that if one of the references yields directly contradictory results, that reference alone can be attacked based on this disclosure. Applicants emphasize that Anderson's teachings are so profoundly contrary to the Applicants' claimed formulations that attacking it alone can indeed provide a basis for overcoming the rejection.

However, for the sake of argument, the Applicants demonstrate below that combining any of the cited references with Anderson still does not render the claimed formulations obvious.

A. Cleuziat

The Examiner cites column 5, line 49 to column 6, line 24, for teaching "the binding of a nucleic acid to a substrate." However, this citation is flawed for the following reasons:

- Cleuziat's teaching is directly contrary to Anderson's disclosure of yeast plasmid DNA not binding to the glass beads. Thus, Anderson and Cleuziat teach away from each other – Anderson does not want binding because of losses of plasmid, while the other discloses that DNA may be bound to insoluble supports. These are contradictory suggestions.

- Cleuziat provides absolutely no guidance as to how to go about effecting the binding. The reason, in part, is that Cleuziat's invention is directed toward a PCR method, and has nothing to do with promoting DNA binding to supports. In contrast, Applicants' claims are directed to a novel formulation that affects both the liberating of DNA from samples, e.g., tissues, food products, etc., as well as its binding to various supports.

The ordinary skilled artisan cannot have used Anderson's DNA *anti-binding* buffer to bind DNA to solid substrates as disclosed by Cleuziat. Accordingly, there cannot be a reasonable expectation of success nor can there be reasonable motivation to combine the teachings.

It is well-settled that "references taken in combination teach away since they produce a seemingly inoperative device." *In re Sponnoble*, 405 F.2d 578, 587 (CCPA 1969). This rule applies here, in that Anderson's DNA *anti-binding* buffer cannot be used to promote binding – i.e., the combination yields an inoperative formulation for binding to solid supports.

In view of the foregoing discussion and the cited Federal Circuit case law, the Applicants respectfully request that the rejections of all claims under § 103(a), based on the combination of Anderson and Cleuziat, be withdrawn.

B. Nochumson

The Examiner repeatedly cites Nochumson for disclosing a low salt elution buffer suitable for releasing DNA bound to soluble supports. Final Action, page 5, 3rd ¶. However, when Nochumson's disclosure is viewed in its entirety, it indisputably expressly teaches away from Applicants' claims, as well as Anderson's *anti-binding* formulation, although for different reasons.

- Anderson expressly teaches non-binding to insoluble supports;
- Nochumson expressly discloses the requirement for chaotropes in order to obtain binding.

In maintaining the rejection, the Examiner has completely ignored Nochumson's disclosure requiring that chaotropic salts be present when binding to insoluble supports. For example, in column 12, lines 14 to15, saturated NaI (a widely used chaotrope) is included in the lysis/binding formulation.

In addition, in column 11 lines 35 to 42, Nochumson states the following:

> More particularly, when DNA-containing gels from electrophoretic chromatography methods are thus treated, ***it is essential that the process be carried out in the presence of one or more chaotropic salts,*** i.e. salts which disrupt the binding of water to agarose or like media, and thus enhance the binding of the DNA to the binding sites, including such salts as NaI, perchlorates, SCN.sup.- salts and the like, but preferably NaI.

This disclosure cannot reasonably be viewed as providing any guidance for developing chaotrope-free lysis/binding formulations for DNA. In accordance with this fact it is settled that if a reference would discourage the skilled artisan from taking a research path, then the reference is teaching away. *In re* Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994). Therefore, in relation to the claimed formulation, Nochumson's disclosure is indisputably, a clear and express teaching away from the Applicants' novel formulations comprising ***anti***-chaotropic salts.

For this reason, Nochumson cannot cure the defects in Anderson, and accordingly these references cannot reasonably be combined.

CONCLUSION

Applicants request entry and consideration of the foregoing remarks.

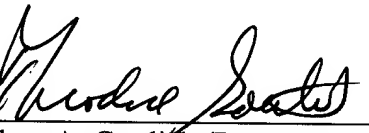
Several factual inaccuracies in the Examiner's analysis have been identified. Therefore, in the interest of advancing the prosecution to a just result Applicants suggest that the remarks herein be considered.

Applicants point out the defects in the Examiner's citation of Anderson, and discuss in great detail why the other references fail to cure these defects.

Accordingly, the rejections of claims 1-5, 7-11 and 26-29 under 35 U.S.C. § 103(a) should be withdrawn.

Respectfully submitted,

NORRIS, MCLAUGHLIN & MARCUS



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